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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/752,343	01/06/2004	Lone Jeppesen	5702.240-US	4231

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EXAMINER	
MCKENZIE, THOMAS C	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 05/31/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/752,343	JEPPESEN ET AL.	
	Examiner	Art Unit	
	Thomas McKenzie, Ph.D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/419,864.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/6/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

5-0-0

DETAILED ACTION

1. This action is in response to an application filed on 1/6/04. There are fifty-four claims pending and fifty-four under consideration. Claims 1-48 are compound claims. Claims 49-51 are composition claims. Claims 52-54 are method of using claims. This is the first action on the merits. The application concerns some dibenzopyran compounds, among others, compositions, and uses thereof.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 52 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The specification does not set forth any steps involved in determining how to identify "conditions mediated the Peroxisome Proliferator-Activated Receptors (PPAR)". It is unclear what diseases and treatments applicant is intending to encompass. Determining whether a given disease responds or does not respond to such a receptor antagonist and thus, covered by the claim language, will require extensive and potentially inconclusive clinical research. With out such clinical research to identify the patients and diseases Applicants intend to treat, the physician skilled in the clinical arts cannot

determine the metes and bounds of the claim. Hence, the claims are indefinite. In the passage spanning line 33, page 3 to line 2, page 4 a number of such conditions are listed. Are these all or are there others?

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-54 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention. The specification is not adequately enabled for the scope of fused rings that have diverse atoms at position X and differing rings sizes. The specification does not enable any skilled pharmacologist or physician to use the invention commensurate in scope with these claims. "The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and

the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546.

a) Determining if any particular claimed compounds with the claimed X linker groups would be active would require synthesis of the substrate and subjecting it to testing with Applicants' two *in vitro* assays. Considering the large number of compounds to be made this is a large quantity of experimentation. b) The direction concerning the claimed compounds is found in lines 13-24, page 5, which merely states Applicants intent to make and use such compounds. c) In the instant case none of the working examples contains any radical X containing nitrogen or a carbonyl group. None of these working examples contain a basic amino or acidic sulfonamide group presently claimed. Only Examples 2 and 3 contain a sulfur atom in radical X. Both Examples 2 and 3 are seven membered sulfur-containing rings, not the six-membered rings presently claimed. Only Examples 4-6 contain an oxygen atom in radical X. Examples 4-6 are seven and eight membered oxygen-containing rings, not the six-membered rings presently claimed. d) The nature of the invention is inhibition of the $PPAR_{\alpha}$ and $PPAR_{\gamma}$ and treatment of human diseases with Applicants' compounds. This involves physiological activity. The nature of the invention requires an understanding of the two PPAR receptors, the binding activity of small ligands to those receptors, and

the ability of those compounds to inhibit activation of the receptor. In view of the unpredictability of receptor binding activity and claimed divergent substituents with varied polarity, size, and polarisability, the skilled physician would indeed question the inclusion of such diverse rings, commensurate in scope with these claims. Also see the MPEP § 2164.03 for enablement requirements in the structure sensitive arts of pharmacology and medicinal chemistry. e) The state of the art is detailed knowledge of the $PPAR_{\alpha}$ and $PPAR_{\gamma}$ receptors is lacking. No X-ray structures of the receptors are known and the structural requirements of ligands to these receptors are poorly understood. The carbonyl group and the amino nitrogen atom of the rejected compounds are hydrogen bond acceptors. The carbon-linker of Applicants working examples is not. The sulfonamide linker of the rejected compounds is acidic. The oxygen, carbon, and sulfur atoms of Applicants working examples are not. The multitude of claimed fused A rings are π-electron deficient. The benzene ring of Applicants working examples is not. There is no reasonable basis for the assumption that the myriad of compounds embraced the present formula (Ia) will all share the same biological properties. For example, the fused rings include pyridine with extra basic sites. The rings include furans with additional polarizable oxygen atoms. The diverse claimed fused heteroaryl rings are chemically non-equivalent and there is no basis in the prior art for assuming in

the non-predictable art of $PPAR_{\alpha}$ and $PPAR_{\gamma}$ receptor pharmacology that structurally dissimilar compounds will have such activity, *In re Surrey* 151 USPQ 724.

f) The artisan using Applicants invention to treat diseases with the claimed compounds would be a physician with a MD degree and several years of experience. He would be unaware of how to predict *a priori* how a changing a heterocyclic ring would affect biological activity. In view of the divergent rings with varied basicity, steric hindrance, and polarisability, the skilled physician would indeed question the inclusion of such fused rings, commensurate in scope with these claims. g) Physiological activity, is well-known to be unpredictable, *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). h) The breadth of the claims includes all of millions of compounds of formula (Ia). Thus, the scope is very broad.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to

make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to practice Applicants' invention.

4. Claims 1-54 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make the compounds of the invention. The passage beginning at line 20, page 65 described various ways the compounds presently claimed could be made. All require stating with compounds of formula II, which have preformed tricyclic rings. In lines 7-8, page 73, Applicants state that all such materials are either commercially available or are known. Yet there are no directions in the specification pointing to the chemical catalogues or journal articles telling how such starting materials may be obtained. According to the U.S. Court of Customs and Patent Appeals in *In re Argoudelis, De Boer, Eble, and Herr* 168 USPQ 99 at 101, "[o]rdinarily no problem in this regard arises since the method of preparing almost all starting materials can be set forth in writing if the materials are not already known and available to the workers in the art, and when this is done the

specification is enabling to the public". *In re Argoudelis, De Boer, Eble, and Herr* 168 USPQ 99 at 104, "it is essential that there be no question that, at the time an application for patent is filed, (emphasis in original) the invention claimed therein is fully capable of being reduced to practice (i.e., that no technological problems, the resolution of which would require more than ordinary skill and reasonable time, remain in order to obtain an operative, useful embodiment)." That is not the situation here. Rather we find very limited direction as to how the many required staring materials of formula II are obtained. For example search of the Aldrich catalog fails to reveal any compounds of formula II with A = fused benzo and Q = O, S or NH, which be required to make Applicants compounds. Search of Chemical Abstracts for a compound of formula II with A = furano, X = $C(O)-CH_2$, and Q = S fails to uncover any mention of this necessary staring material. Where may the directions to prepare or buy it be found? The scope of the claimed compounds embraces hundreds of different core rings embraced by the present set of A, X, and Q variables.

5. Claims 49-54 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to enable any physician skilled in the art of medicine, to make the invention commensurate in scope with

these claims. The how to make requirement of the enablement statute, when applied to process claims, refers to operability and how to make the claimed process work. The four main issues are the lack of any correlation between clinical efficacy for any disease treatment and Applicants' two *in vitro* assays, the lack of any working examples, the state of the prior art, and the breadth of the claims. The factors to be considered in making an enablement rejection have been summarized above.

There are two *in vitro* assays, drawn to binding to the $PPAR_{\alpha}$ and $PPAR_{\gamma}$ receptors, described in lines 14-30, page 74 with no data on any compounds. Applicants do not state and it is not recognized in the therapeutic arts this assay is correlated to clinical efficacy for the treatment of any diseases. The state of the clinical arts in $PPAR_{\alpha}$ and $PPAR_{\gamma}$ receptor related diseases is provided by Cobb (Ann. Reports Med. Chem.) that antidiabeteic efficacy has been correlated to affinity to the PPARγ binding site, in the first paragraph, page 216. Sapone (Pharmacogenetics) reports that mice lacking any PPARα receptors develop normally. In his abstract he says that "[t]he biological significance of these novel PPARalpha alleles remains to be established"..

None of Applicants working examples fall within the currently claimed scope. The scope of the claims involves all of the thousands of compounds of

claim 1 as well as the unknown list of diseases embraced by the term "conditions mediated the Peroxisome Proliferator-Activated Receptors (PPAR)". There are dozens of such receptors in addition to the $PPAR_{\alpha}$ and $PPAR_{\gamma}$ for which Applicants have a screening assay. Thus, the scope of claims is very broad.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

Claims 52-54 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for preventing diseases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Applicants are not enabled for preventing any of these diseases. The only established prophylactics are vaccines not the dibenzopyran compounds such as present here. In addition, it is presumed that "prevention" of the claimed diseases would require a method of identifying those individuals who

will develop the claimed diseases before they exhibit symptoms. There is no evidence of record that would guide the skilled clinician to identify those who have the potential of becoming afflicted.

The factors to be considered in making an enablement rejection have been summarized above. 1) As discussed above, preventing diseases requires identifying those patients who will acquire the disease before a disease such as diabetes occurs. This would require extensive and potentially opened ended clinical research on healthy subjects. 2) The passage spanning line 33, page 3 to line 2, page 4 lists the diseases Applicant intend to treat. 3) There is no working example of such a preventive procedure in man or animal in the specification. 4) The claims rejected are drawn to clinical medicine and are therefore physiological in nature. 5) The state of the art is that no general procedure is art-recognized for determining which patients generally will become diabetic say before the fact. 6) The artisan using Applicants invention would be a Board Certified physician in endocrinology with an MD degree and several years of experience. Despite intensive efforts, pharmaceutical science has been unable to find a way of getting a compound to be effective for the prevention of PPAR related diseases generally. Under such circumstances, it is proper for the PTO to require evidence that such an unprecedented feat has actually been accomplished, *In re Ferens*, 163 USPQ 609.

No such evidence has been presented in this case. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs. Novo Nordisk*, 42 USPQ2nd 1001, 1006. This establishes that it is not reasonable to any agent to be able to prevent PPAR related generally. That is, the skill is so low that no compound effective generally against such disorders has ever been found let alone one that can prevent such conditions. 7) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). 8) The claims broadly read on all patients, not just those undergoing therapy for the claimed diseases and on the multitude of compounds embraced by Formula (Ia).

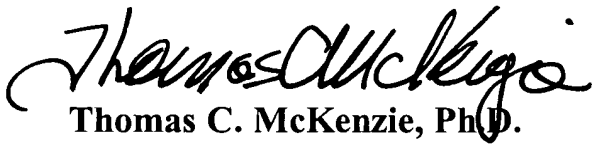
The Examiner suggests deletion of the word "preventing".

Conclusion

6. Information regarding the status of an application should be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system,

contact the Electronic Business Center (EBC) at (866) 217-9197 (toll-free). Please direct general inquiries to the receptionist whose telephone number is (703) 308-1235.

7. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (571) 272-0670. The FAX number for amendments is (571) 273-8300. The PTO presently encourages all applicants to communicate by FAX. The Examiner is available from 9:00am to 5:30pm, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, please contact James O. Wilson, acting SPE of Art Unit 1624, at (571)-272-0661.



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